

REMARKS

Claims 1-48 were pending in the present application and claims 1-22 are under consideration. By virtue of this response, claims 24-48 have been canceled, claims 1-3 and 17-19 have been amended, and new claims 49-68 have been added. Accordingly, claims 1-22 and 49-68 are currently under consideration. Amendment and cancellation of certain claims is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented.

The amendments to the claims find support in the specification. The amendment to claim 1 finds support, *inter alia*, in original claim 3. The amendments to claims 2 and 3 find support, *inter alia*, at page 13, lines 1-3 of the specification. Support for the amendment to claim 17 is replete in the specification (e.g. the Examples) and in the recitation of the term "sequence tagged site" in original claim 17. Support for the amendments to claims 18 and 19 and for new claims 49 and 68 is replete in the specification (see, e.g., Examples 1 and 2). New claims 50-59 and 60-67, depending from new claim 49, correspond to claims 2-11 and 14-21, respectively, and are supported by the original claims and/or in the specification as described *supra*.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

I. Rejections under 35 U.S.C. § 112, First Paragraph

Claims 1-22 were rejected under 35 U.S.C. § 112, first paragraph. The Office asserted the specification does not enable the reader to identify probes with a defined chromosomal location and does not provide hybridization conditions for probes.

Applicants respectfully disagree. Preparation and use of the claimed arrays is well within the skill of a scientist guided by the specification. One of ordinary skill guided by the specification would have no difficulty identifying sequences with a known chromosomal location (e.g., location of a gene on a particular chromosome or a particular chromosomal locus). At the time the application was filed such information was readily available, and additional information has become available since filing. The specification clearly describes the use of public databases such as GenBank, EMBL, DDBJ, PDB, SWISS-PROT, EST, STS, GSS, and HTGS which include this information. For example, an exemplary STS database is referred to at page 31 of the specification. It is well established that a patent specification need not teach, and preferably omits, what is well known in the art. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986). The specification provides ample guidance concerning the claimed arrays (see, e.g., page 7, lines 15-18, and page 11, line 24 to page 13, line 6).

In the case of claim 18, the Office asserts (1) that the specification does not provide a defined chromosomal location for the probes defined by the recited primer pairs and (2) the probes defined by these primer pairs "are useless without defining some chromosomal location and/or possible linkage to a genetic disease locus." As to (1), in addition to the ready availability of information about the STSs defined by these primer pairs from the sources discussed above, Table 1 additionally provides STS names and accession numbers for the primer pairs. One of skill would have no difficulty obtaining information about these STSs or their corresponding genes. As to (2), Applicants do not agree that chromosomal location and/or possible linkage to a genetic disease locus is required for the utility of the arrays. For example, the arrays can be used to screen for differential gene expression among multiple subjects (see, e.g., Abstract, specification at page 5, lines 1-14).

Finally, the Office acknowledges that a variety of hybridization conditions are discussed in the specification, but asserts that the use of the claimed arrays is not enabled because specific hybridization conditions for each probe are not taught, i.e., because "each probe sequence is generally different which required different hybridization conditions for the same stringency." Applicants respectfully disagree. If each probe required a different hybridization condition, array technology itself would be impractical, which is clearly not the case. Applicants submit that, provided with the guidance of the specification and knowledge in the art, it is well within the ability of the skilled practitioner to use the arrays of the invention with no undue experimentation. Applicants note that with regard to hybridization technology, the level of skill in the art is high and the physical parameters of hybridization are fairly well known and predictable. This invention can be made and used without undue experimentation.

II. Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 18-22 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 has been amended to increase clarity.

Claim 19 has been amended to increase clarity by noting that the target-probe complex is formed by hybridization. The hybridization complex can, of course, be stabilized by chemical cross-linking and other means.

III. Rejections under 35 U.S.C. § 103(a)

Claims 1-7, 9-17, and 19-22 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable in view of Duggan et al. *Nat. Genetics* 21 (Suppl.):10(1999) in

view of Schena et al., *Science* 270:467 (1995), taken further in view of Wilcox et al., *Nuc. Acids Res.* 19:1837 (1991). Claims 1-17 and 19-22 were rejected under 35 U.S.C. § 103(a) as being unpatentable in view of Duggan et al., Schena et al., and Wilcox et al., and in view of Fodor et al. (Pat. 5,510,270). Applicants respectfully traverse.

The Cited Art

1. Duggan et al.

Duggan et al. reviews the making and use of microarrays of cDNA probes. The Office notes that Duggan et al. describes formulating microarrays with polynucleotides of from 600 to 2400 bases in length. The Office stated that this range is "deemed to overlap with the range of 50 to about 500" nucleotides as recited in claim 1. Duggan et al. notes arrays may include cDNAs that contain 3' untranslated sequences.

2. Schena et al.

Schena et al. describes expression profiles using cDNA arrays. Specifically, Schena et al. described microarrays prepared by high-speed robotic printing of *Arabidopsis* cDNAs on glass, and are used for quantitative monitoring of gene expression patterns. The cDNAs of the array described by Schena et al. averaged 1.0 kb in length and included "14 complete sequences" and "31 ESTs." The Office notes that the labeled polynucleotides used by Schena et al. to probe the immobilized cDNAs included 3' sequences¹

¹ It appears the Office may have incorrectly equated the labeled hybridization probes described in footnote 5 of Schena et al. and the immobilized probes of the instant invention (see page 7, lines 1-5 of the Office Action). Although the term "probes" is used in both

3. Fodor

Fodor is cited as describing arrays in which immobilized "probes" are localized in a predetermined region having the dimensions recited in instant claim 8.

4. Wilcox et al.

Wilcox et al. described a mapping strategy in which primer pairs defining gene-specific sequence-tagged sites (STSs) are used to amplify human sequences in panels of human-hamster somatic cell hybrids, thereby assigning the STSs to specific chromosomes or chromosome regions. Wilcox et al. does not teach or suggest arrays. Wilcox et al. is relied on by the Office to show the presence of 3'-untranslated sequences in cDNAs made by "oligo(A) primed synthesis."²

The Traverse

The Office asserts that it would have been obvious to "practice the arrays of Duggan et al. as further detailed in Schena et al., with poly(A) primed probes which contain 3'untranslated regions of transcripts as verified in Wilcox et al. thus resulting in the practice of the instant invention."

Applicants respectfully maintain that no *prima facie* case of obviousness has been established by the Office. To establish *prima facie* obviousness, the Office must indicate where the prior art provides reason or motivation for one of skill to make the claimed composition or carry out the claimed method. The Office must also demonstrate that one of ordinary skill would have had a reasonable expectation of success in attempting to make the composition or carry out the method. *In re Vaeck*,

cases, the immobilized probes of the invention and labeled probes of Schena et al. (representing heterogeneous transcripts derived from total RNA) are entirely different.

² It is understood by the Applicants that "oligo dT" primed synthesis is intended.

20 USPQ2d 1438 (Fed. Cir. 1991). In determining obviousness the reference must be read without benefit of applicants' teachings.

The basis for the rejection of claims set forth by the Office is it allegedly would have been obvious to "practice the arrays of Duggan et al. as further detailed in Schena et al, with poly(A) primed probes which contain the 3'-untranslated region of transcripts." In articulating the rejection, the Office noted "the instant probes are not limited to being 'only' targeted to the 3' untranslated section of the target transcripts."

First, the alleged relevance of Duggan et al. was based, at least in part, on the assertion by the Office that the size range of "from 600 to 2400 bases in length" was deemed to overlap the range of "about 50 to about 500" nucleotides as was recited in claim 1. For clarity of the record, the Office is respectfully asked to explain why two nonoverlapping ranges are deemed to overlap. The amendment of claim 1 to recite a range of about 50 to 500 nucleotides clearly overcomes this basis for the rejection, as does the recitation in amended claims 2 and 3 of even shorter probes. Nothing in Duggan et al., alone or in combination with the other cited references, suggested an array of short probes complementary to the 3' untranslated sequences of gene transcripts. At best, Duggan et al. described that long cDNA probes on arrays may incidentally include 3' untranslated regions along with coding regions.

Thus, nothing in the Duggan reference taught or suggested the present invention.

The Office stated "It is noted that the instant probes are not limited to being 'only' targeted to the 3' untranslated section of the target transcripts." Applicants maintain that the selection of short probes complementary to the 3' untranslated sequences of gene transcripts, and the recitation that the arrays comprise at least 100 such probes renders the claimed arrays nonobvious. Further, new claims 49 and 68 recite that each polynucleotide probe of the plurality (comprising at least 100 polynucleotides that are each complementary to a distinct gene transcript) is complementary to only the 3' untranslated sequence of a gene transcript, specifically addressing the concerns of the Office. It is noted that the Schena et al. article cited in

Duggan and relied on by the Office teaches that full-length cDNAs should be used as probes and, further, all of the ESTs cited by Schena et al. for which a GenBank alignment to cDNA is available (i.e., all ESTs except one³) included protein coding sequences and were not limited to 3' untranslated sequences.

In summary, nothing in the cited references taught or suggested the present invention. Applicants respectfully request that this rejection be withdrawn.

IV. Objections and Other Matters

A. Title

The Office states that a new title is required that is clearly indicative of the invention to which the claims are directed. Applicants wish to defer any amendment of the title until they have received an indication that claims are allowable, thereby permitting the most appropriate title to be selected.

B. "Embedded hyperlink"

Applicants do not intend the web addresses on pages 12 and 31 to be active hyperlinks. They are citations to databases. To the extent that the recitation of a web addresses at page 12 and page 31 are considered by the Office to be "embedded hyperlinks," Applicants refer to MPEP 608.01, which states, in part "[When] applicant does not intend to have these hyperlinks be active links, examiners should not object to these hyperlinks. The Office will disable these hyperlinks when preparing the text to be loaded onto the USPTO web database." In the interest of expediting prosecution, applicant has reformatted the web address. However, Applicants respectfully request that the Office reconsider the objection to disclosure

³ Applicants did not find a cDNA corresponding to the Schena et al. EST83 in Genbank.

so that the specification can be made clearer by using a standard form for the web addresses.

C. Footnotes

The Office states objected to the footnotes on pages 12 and 13. The specification has been amended to incorporate the footnotes into the body of the specification.

D. Replacement pages

The Office requested replacement pages for pages 32-35. These pages are enclosed. No new matter is added.

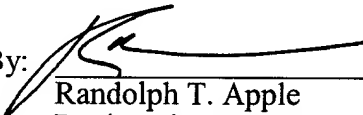
CONCLUSION

Applicant has, by way of the amendments and remarks presented herein, made a sincere effort to overcome rejections and address all issues that were raised in the outstanding Office Action. Accordingly, reconsideration and allowance of the pending claims are respectfully requested. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 421452000100.

Respectfully submitted,

Dated: October 18, 2002

By: 
Randolph T. Apple
Registration No. 36,429

Morrison & Foerster LLP
755 Page Mill Road
Palo Alto, California 94304-1018
Telephone: (650) 813-5933
Facsimile: (650) 494-0792

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

On page 12, please replace the paragraph beginning on line one with the following:

Sequence alignment and homology searches are often determined with the aid of computer methods. A variety of software programs are available in the art. [Non-limiting examples of these programs are Blast¹, Fasta², DNA Star, MegAlign, and GeneJockey.] Non-limiting examples of these programs are Blast (available on the worldwide web at [http://www. followed by ncbi.nlm.nih.gov/BLAST/](http://www.followedbyncbi.nlm.nih.gov/BLAST/)), Fasta (Genetics Computing Group package, Madison, Wisconsin), DNA Star, MegAlign, and GeneJockey. Any sequence databases that contains DNA sequences corresponding to a gene or a segment thereof can be used for sequence analysis. Commonly employed databases include but are not limited to GenBank, EMBL, DDBJ, PDB, SWISS-PROT, EST, STS, GSS, and HTGS. Sequence similarity can be discerned by aligning the probe sequence against a DNA sequence database. Common parameters for determining the extent of homology set forth by one or more of the aforementioned alignment programs include p value and percent sequence identity. P value is the probability that the alignment is produced by chance. For a single alignment, the p value can be calculated according to Karlin et al. (1990) *Proc.Natl. Acad. Sci* **87**: 2246. For multiple alignments, the p value can be calculated using a heuristic approach such as the one programmed in Blast. Percent sequence identify is defined by the ratio of the number of nucleotide matches between the query sequence and the known sequence when the two are optimally aligned. A probe sequence is considered to have no substantial homology when the region of alignment exhibits less than 20% of sequence identity, more preferably less than 10%

¹~~Blast~~ is available from the world wide web at <http://www.ncbi.nlm.nih.gove/BLAST/>.

²~~Fasta~~ is another alignment algorithm, available in the Genetics Computing Group package, Madison, Wisconsin, U.S.A.]

identity, even more preferably less than 5% identity using Fasta alignment program with the default settings.

At page 31, please replace the paragraph beginning on line 4 with the following:

Sequence-tagged site (STS) probes (hereinafter STS tags) are generated by amplifying human genomic DNA using selected primer pairs. The selected primer pairs yield amplified sequences corresponding to the 3' untranslated region of gene transcripts of particular interest. A list of exemplary primer pairs and the resultant gene sequences are summarized in Table 1. Additional primer pairs may be obtained from worldwide web at [<http://www.ncbi.nlm.nih.gov/dbSTS/index.html>] [http://www.followed by ncbi.nlm.nih.gov/dbSTS/index.html](http://www.followedby.ncbi.nlm.nih.gov/dbSTS/index.html) or related web sites. Each PCR reaction contains approximately 100 pmoles of each primer, 50 ng human genomic DNA, and other reagents included in Advantage Genomic PCR kit (Clontech). The PCR reaction is carried out according to manufacturer's instructions which yields approximately 5 ug of each STS tag. The resultant STS tags are analyzed, sequenced, purified, and concentrated by lyophilization (Savant) to approximately 2 ug/ul. Samples of concentrated STS tags are aliquoted and stored at low temperature for future use.

In the Claims:

Please cancel claims 24-48.

Please amend claims 1, 2, 3, 17, 18 and 19 as follows:

1. (Amended) An array comprising a plurality of polynucleotide probes immobilized on a solid support, wherein:

(a) the plurality of polynucleotide probes corresponds to a multiplicity of gene transcripts and comprises at least 100 polynucleotides that are each complementary to a distinct gene transcript;

(b) each polynucleotide probe of the plurality is localized to a predetermined region on the solid support;

(c) each polynucleotide probe of the plurality is from about 50 to [about] 500 nucleotides in length;

(d) each polynucleotide probe of the plurality is complementary to 3' untranslated sequence of a gene transcript, said untranslated sequence having a defined chromosomal location.

2. (Amended) An array of claim 1, wherein each polynucleotide probe of the plurality of polynucleotide probes is from about 50 to 400 nucleotides in length [comprises at least about 20 polynucleotides, each being complementary to a distinct gene transcript].

3. (Amended) An array of claim 1, wherein each polynucleotide probe of the plurality of polynucleotide probes is from about 50 to 300 nucleotides in length [comprises at least about 100 polynucleotides, each being complementary to a distinct gene transcript].

17. (Amended) An array of claim 1, [where the] wherein each polynucleotide probe of the plurality [of polynucleotide probe comprises sequence-tagged site (STS) tages] is prepared by amplification of genomic DNA or cDNA using a pair of primers that amplify the region corresponding to 3' untranslated sequence of a gene transcript.

18. (Amended) An array of claim 1, wherein [each] the array comprises a polynucleotide probe prepared by amplification of genomic DNA or cDNA [is amplified] using a primer pair selected from the group consisting of SEQ ID NOS. 1-2, 3-4, 5-6, 7-8, 9-10, 11-12, 13-14, 15-16, 17-18, 19-20, 21-22, 23-24, 25-26, 27-28, 29-30, 31-32, 33-34, 35-36, 37-38, 39-40, 41-42, 43-44, 45-46, 47-48, 49-50, 51-52, 53-54, 55-56, 57-58, 59-60, 61-62, 63-64, 65-66, and 67-68.

19. (Amended) An array of claim 1 further comprising target polynucleotides corresponding to gene transcripts expressed in a subject, wherein the target polynucleotides are bound to the polynucleotide probes in form of stable target-probe hybridization complexes.

Please add new claims 49-68.

Table 1: STS Tags and Exemplary Primer Pairs

	GENE	STS NAME	STS acc #		SEQ ID NO:
1.	Glucokinase regulator (GCKR)	SHGC 35430	G 29810	Forward Primer: AACCCATGTTTCTGGGTGG Reverse Primer: CGGTGAGAGTAGAAACCACTAGG	1 2
2.	Interleukin receptor, type II precursor	WI 11083	G22557	Forward Primer: TTTCATTTATTTCACCTGGGATAGG Reverse Primer: CTTGGTTTTGGGGGAATAT	3 4
3.	Inteleukin1 receptor, type I precursor	SHGC 35324	G28576	Forward Primer: GCCAAGAGTTCTTTAGGTGCC Reverse Primer: TTTTAAAGATCTTCCCAAGCC	5 6
4.	Human insulin-like growth factor binding protein-5 (IGFBP5)	SHGC 11498	G14572	Forward Primer: GAATTAAATGAGGGCTGAAACG Reverse Primer: CATGTGCATATTTTCATTCCCC	7 8
5.	Protein Phosphatase 1, catalytic subunit, beta ispfom (PPP1CB)	WI 7312	G06545	Forward Primer: ATGTGATTATGTGTACCTTGGC Reverse Primer: AATCGTATACAAACATTACATGGC	9 10
6.	Human Protein tyrosine phosphatase	WI 9369	G07262	Forward Primer: TGGACATTTCATACCTGTGCA Reverse Primer: ACCTACCCTGAGGTCCGTCT	11 12
7.	Hexokinase-1 (HK1)	SHGC 11749	G14649	Forward Primer: TTTCTTTTATTGGGAAAAGTCAGC Reverse Primer: TGCTAACCCCGTCTGCTC	13 14
8.	Arachidonate 5-lipoxygenase (ALOX5)	WI 9162	G07156	Forward Primer: TTCCATTTATTCTTTTGATCTTCAGG Reverse Primer: GCTGGGTGTGACAGGAC	15 16

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9.	Protein tyrosine phosphatase 2C	SHGC 30316	G27080	Forward Primer: CTAGAAGACAGCAGTGACACTTCC Reverse Primer: TGGGGTAGTTTGGCTGCC	17 18
10.	Placental Protein II precursor	SHGC 9798	G11327	Forward Primer: GGAGAGGACTGGAAAGGGATC Reverse Primer: TGCCAAAATTCTAGAGGATAAAGG	19 20
11.	Insulin like growth factor 1 (somatomedia C) (IGF1)	WI 7033	G06363	Forward Primer: ACAGGAGGATTAAACAGACAGAGAGG Reverse Primer: TTATTTAATTGTGTTTTAGAGGGCA	21 22
12.	Human Protein tyrosine Kinase	WI 9296	G07226	Forward Primer: TGCTGCATAAATCACTTATCGG Reverse Primer: GAACACAAATTTCTGAAAGGTGC	23 24
13.	Glycogen synthase (human liver)	WI 7963	G06781	Forward Primer: CATGTGCTGCATGAAGAGCT Reverse Primer: AAGCTGCATAAATAGTAAGCAAAAGG	25 26
14.	Protein tyrosine Phosphatase	SHGC 31640	G27089	Forward Primer: TAATCAAATTAACCCACCCCAAGG Reverse Primer: GCCTTAGGCTGTGTGATAAAACC	27 28
15.	Mannose receptor (M6PR)	WI 7191	G06444	Forward Primer: ATAAATTGCTTGTGTTTTCTAGCCTGG Reverse Primer: TAATTGGAGTGGAAAATAAAAAGTGG	29 30
16.	Glutathione S-transferase, microsomal	WI 7728	G06674	Forward Primer: ACAACTCAACATCCAGTTGGC Reverse Primer: TTCATGTCTGTTTCAGCAGTATTG	31 32
17.	Glucose trasproter type 3, brain	SHGC 31620	G27088	Forward Primer: CAGGATGAACCCAGGACG Reverse Primer: GGCAAAAGTTGTCATGTGCC	33 34
18.	Protein phosphatase 4 (formerly	WI 9235	G07192	Forward Primer: TTCCTCAGACGGAGGCTG	35

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	x) catalytic subunit (PPP4C0			Reverse Primer: GGAACATGGAGCTAGGTCTCC	36
19.	Low density lipoprotein receptor precursor	SHGC15376	G15092	Forward Primer: GTTTAAAAAGTGACACCCATCTCC Reverse Primer: TGCCTCTGAAATGCTCTCTC	37 38
20.	Lecithin cholesterol acyltransferase	WI 10276	G11801	Forward Primer: TTATTGGTGGTGTCTGATGAGC Reverse Primer: GGCTTCATCTCTCTTGGGG	39 40
21.	Interleukin 4 receptor (IL4R)	WI 9023	G07084	Forward Primer: AAAACTGAGGCCCTTGGG Reverse Primer: ATGCCCTTGGGCGAGTTACAAC	41 42
22.	Regenerating islet-derived-1 alpha (pancreatic stone protein, pancreatic thread protein) (REG1A)	WI 9197	G07172	Forward Primer: CATCTCTCCAACTCAACTCAACC Reverse Primer: TTTAGGGTTCCAAAGACTGGG	43 44
23.	Interleukin1, beta (IL1B)	WI 7848	G05863	Forward Primer: TTCTGAAAAATATAACCAGCCATTG Reverse Primer: ACCATTTCACATTTATTTGAAAGC	45 46
24.	Insulin like growth factor binding protein 5 (IGFBP5)	SHGC 11498	G14572	Forward Primer: GAATTAATGAGGGGCTGAAACG Reverse Primer: CATGTGCATATTTTCATTCCCC	47 48
25.	Insulin receptor substrate-1 (human skeletal muscle)	WI 9260	G07206	Forward Primer: GTGACACCCAGAAATATGAGTCTGC Reverse Primer: AACCCATTCTCTCATGACACG	49 50
26.	Alkaline phosphatase, placental (Regan isoryme) (ALPP)	WI 8964	G07054	Forward Primer: AGTCATGGCAGCACCTGAG Reverse Primer: ACCACAGCAGCCTCCTTG	51 52

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27.	Human DNA dependent protein kinase catalytic subunit (DNA-PKCs)	SHGC 35517	G29848	Forward Primer: CTTGGTTGGCAGCATTC Reverse Primer: TGACTTAATACTTTGGTAAGCCTGG	53 54
28.	Lipoprotein lipase (LPL)	WI 9031	G07089	Forward Primer: TTACAAAACATACCCAGTGTGG Reverse Primer: CTTTTAGTGCTTGAGACTGTCTCC	55 56
29.	Human MAP kinase phosphatase (MKP-2)	SHGC 35388	G28599	Forward Primer: GCAGAAAGTTGGGACTGAGC Reverse Primer: TGAAACTGACACATAAACCAACC	57 58
30.	Protein Kinase C, theta type	SHGC 9690	G11293	Forward Primer: CCCCATGTGACTTTATCTGTAGC Reverse Primer: AGTCTTGAGACGTCTGTACTCCG	59 60
31.	Insulin degrading enzyme	UTR 9770	G13262	Forward Primer: ATTCCTGAGTCTTCCAGAGCC Reverse Primer: ATGACATTTGACAAATTTTGTGTTG	61 62
32.	Phosphofructokinase, muscle (PFKM)	WI 7025	G06359	Forward Primer: TCCACATCTTCTCAGTGTTTTAGC Reverse Primer: TCACAGTGACCAGTTGGCAT	63 64
33.	ATP synthase lipid binding protein P2 precursor	SHGC 10801	G13455	Forward Primer: CCCGTGTGTTCCCTTTTCCTA Reverse Primer: AGGCACTCAGCCCAACTGTG	65 66
34.	Mevalonate kinase	A001U02	G19646	Forward Primer: GTACAGATCGGAAGAAAGT Reverse Primer: CCTCCCTTCTACCTAAC	67 68

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